health management, the natural bias is actually towards pessimism. And this is precisely why it takes a dose of contrived optimism, riding on fake treatment, to restore confidence in the wisdom of self-cure.

A Keynesian twist

We likened the health governor to a hospital manager who has to manage the economics of health care. We'll end with a rather different economic analogy for placebo medicine as an antidote to an over-cautious pessimistic regime.

Imagine you are the Finance Minister of a country dependent on manufacture for creating wealth. And let's assume your main market is the domestic one. Then, for your country's economy to remain in good shape, your manufacturers must be able to sell their goods to your own citizens. So it is essential that your citizens, first do not save too much, and second spend what money they have on home-made goods. Now, suppose something bad happens beyond your borders which, though it doesn't yet directly affect things at home, makes everybody jittery about the future. Motivated by anxiety, your citizens start saving rather than spending, so as to make sure they have enough in reserve in case things get worse. The result is that your country's economy is headed for recession.

How then can you as Finance Minister get the economy back on track? The answer was proposed by the economist J.M. Keynes. What you have to do to is to artificially boost demand at home by *pretending* that things are going to be all right. And, just to the extent that the original refusal of your citizens to spend was unjustified by any objective threat, this solution will work.

So, Keynes discovered a placebo solution to the problem of wealth creation for a country whose citizens are inclined to conserve resources when they don't need to. But our real point is that human culture discovered a Keynesian solution to the problem of health creation for human bodies whose healing systems were designed to play too safe.

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Features

The ancestor's paunch

The obesity problem in the industrialized world is a recent phenomenon, potentially owing to a confluence of factors, most notably an abundance of fatty, sugary foods. But does our evolutionary past have any part to play? **Cyrus Martin** explores the role of diet in human evolution and current evolutionary theories explaining the obesity epidemic.

Our collective waistlines are expanding. The incidence of obesity in the US has risen to such levels that officials have resorted to drastic measures, as seen in mayor Michael Bloomberg's recent proposal of banning the sale of oversized sodas in New York City. This is in a country where government meddling in personal lives is fought tooth and nail, highlighting the extent of the crisis. If one looks at US adults, the overweight and obese comprise nearly 80% of the population. And a global survey shows that the obesity problem is rapidly worsening in nearly all industrialized nations, particularly in Europe but with Asia following closely behind. This trend should command society's attention as obesity is closely linked to a host of diseases, especially diabetes, cardiovascular disease and cancer. Obesity is in fact the second leading cause of cancer next to smoking. So how can we account for this obesity 'epidemic', as it is frequently referred to? Here, we are constantly reminded that the roots of obesity are two-fold: a sedentary lifestyle coupled with an abundance of fatty, sugary foods. But what if the question is approached from an evolutionary perspective? Is it possible that our history as a species can throw some additional light on the problem?

Diet and human evolution

Before tackling the specific question of obesity, it's instructive to consider what we know about the role of diet in shaping human evolution. One consistent theme in this area of evolutionary biology is the role of cultural innovations. There is good evidence, for example, that the use

of fire for cooking led to a suite of adaptations in the ancestors of modern humans, including smaller teeth and jaws, and a shorter intestine. Cooking was highly advantageous, as cooked food is easier to chew and swallow. And once in the gut, cooked food is more easily absorbed. Thus a greater caloric benefit is received and total time spent chewing and digesting is reduced, both of which would give considerable energetic benefits. Furthermore, we can understand how cooking would have, for example, led to a reduction in tooth size, as the high mechanical forces generated by large teeth that are required to chew raw food would have no longer been necessary.

A particularly extreme case of human evolution in response to diet is the pygmy phenotype. The term 'pygmy' refers to various groups of short-statured hunter-gatherer populations living in tropical rainforests around the world. The short stature phenotype is, however, not caused by environmental factors like malnutrition but rather has a genetic basis. Small body size in pygmies has evolved multiple times in similar rainforest habitats, which supports the view that the pygmy phenotype evolved via natural selection. But what might be the adaptive value of a small body size? One possibility is that nutrient limitation, as is characteristic of the pygmies' environment, may have conferred an advantage to smaller bodies, which require fewer calories. Nonetheless, there are other plausible explanations for the evolution of small body size, such as improved thermoregulation, and multiple factors have probably worked together to produce the pygmy phenotype.

Perhaps the best understood example of diet shaping recent human evolution is the case of lactase persistence. Lactase persistence allows the digestion of milk past weaning and allows adults to use animal milk as a food. Lack of this trait, as seen in those unfortunate individuals that are lactose intolerant, results in diarrhea if dairy is consumed. The trait, which is conferred by changes in the regulatory DNA sequences controlling lactase expression, evolved with the domestication of animals for dairying at the start of the Neolithic, and spread from the fertile crescent in the Middle East westward into Europe. Variants in the lactase gene that allow prolonged expression of the enzyme have been under positive selection in Europeans. However, lactase persistence is also common in east African populations, but in this case the lactase variants are different, suggesting that there lactase persistence evolved independently.

Obesity seen as evolutionary discord

The above examples clearly demonstrate how food — whether it be the type of food, its availability, or how it is processed — can shape the evolution of our species. But what does this have to do with disease and specifically obesity? One possibility is that our modern environment has significantly changed from the environment in which we evolved such adaptations, resulting in a genotype–environment mismatch. A classic example of this is sickle cell anemia, in which a variant of the hemoglobin gene causes mis-shaped red blood cells, leading to a range of health problems for the carrier. While deleterious for most people, the gene variant has been maintained in African populations because it confers protection from malaria in individuals carrying one copy of the sickle-cell gene. In African-Americans, however, the threat of malaria has been lifted, but the gene variant persists as a relic of the

The causes of obesity: The composition of our modern diets, particularly an emphasis on high fat and sugar, may alter the homeostatic mechanisms regulating body weight. (Photo: Norman Hollands/Getty Images/Photolibrary collection.)

Diet and human evolution: The type of food, its abundance, and its handling have all had important roles in human evolution. In the case of cooking (top left, photo: Lee Frost/Getty Images), thermal food processing allowed our teeth to become much smaller and made the feeding process more efficient, thus freeing up time to pursue other activities. Furthermore, a lack of food, as seen in the rainforest habitats occupied by modern-day pygmies (bottom left, photo: Nigel Pavitt/Getty Images), may have led to the evolution of smaller body sizes, which require fewer calories. And in the case of lactase persistence, a new trait has evolved in response to the introduction of a novel food item — milk (right, photo: Picavet/Getty Images).

evolutionary past, haunting carriers with the disease.

Interestingly, popular culture has taken hold of this notion that our evolutionary makeup is ill-suited to our modern environment. Consider, for example, the barefoot running craze, which was touched off by popular books and several scientific papers proposing that man has evolved to run barefoot and that modern running shoes discourage a natural gait, potentially leading to injury. And not only are we being encouraged to run like a caveman, there are proponents of a theory that we should eat like one, too, as embodied in the paleodiet. Here we begin to see how an evolutionary perspective could in principle help understand the obesity epidemic.

In the Paleolithic era, the phase of human prehistory ending with the advent of agriculture about 10,000 years ago, humans lived in small groups of hunter-gatherers, living on a diverse diet of small and large game (including carrion), fish, vegetables, tubers, fruits, and nuts. Lacking were the grains and legumes, not to mention refined sugars and oils, seen in modern diets. Today, practitioners of the paleodiet subscribe to the view that the human body is adapted to eat only items on the paleomenu, and that our modern food pyramid with grains at the base doesn't match our physiology.

Work in animals suggests there may be some wisdom behind the principle that the composition of our diet, not just the seemingly trivial explanation that we are eating more, could have a profound effect on body weight. Most notably, the mouse model has allowed a detailed understanding of the internal signals and circuitry that maintain body weight at a stable set point. A high-fat diet impinges on these pathways, rendering the animal less sensitive to

satiety signals, resulting in overeating and other metabolic changes. And it seems likely that the palatability of high-fat food factors heavily. After all, fat is flavor! In this scenario then, diet composition is the underlying causative factor, with over-eating being a secondary consequence.

Thrifty and drifty genes

While the proponents of various diet fads are often amateur scientists at best, often with a commercial interest, serious academics have theorized about the potential role of our evolutionary history in the modern obesity epidemic. Notably, in 1962 James Neel — who, coincidentally, also helped show that sickle cell anemia was an inherited disease — wrote an influential article for the *American Journal of Human Genetics*, entitled 'Diabetes Mellitus: A Thrifty Genotype Rendered Detrimental by Progress'. Neel's idea at the time was that humans may have evolved a so-called 'thrifty' genotype in which excess nutrients, when available, are ingested and stored as fat that becomes advantageous during times of want. Put in a modern, industrialized setting, in which famines are rare and food is plentiful, this genotype would generate perpetual obesity and its ensuing health problems.

The original thrifty gene hypothesis posited that hunter-gatherers would have been exposed to food shortages, favoring the spread of thrifty genes. In a recent debate on the evolutionary origins of obesity (Int. J. Obes. (2008), *32*, 1607–1610), however, Andrew Prentice and colleagues argued that famines did not exert a selective pressure on humans until relatively recently, ironically beginning with the advent of agriculture at the start of the Neolithic. Before agriculture was invented, hunter-gatherers presumably foraged over a wide geographic area and didn't depend heavily on local conditions, Prentice *et al.* argue. The introduction of agriculture, by contrast, created geographically rooted populations, exposing them to the risk of environmental variability. Others, however, offer a more nuanced view. Peter Bellwood, an archaeologist at the Australian National University who has published extensively on the origins of agriculture, says, "I would caution against using the long-lived anthropological belief, allied to the concept of 'affluent foragers', that hunters always had sufficient food and farmers were always subject to food shortages. Many early farmers were very healthy — poor health developed later as crowding increased, but early farmers had more food than most hunters." Bellwood adds, "Furthermore, during the 2 million years of hunter-gatherer prehistory, foraging groups would have suffered immensely from the major swings in Pleistocene climate, especially in regions subject to glaciation, desertification, drowning by rising sea levels, etc. Early farmers carried a 'portmanteau' of domesticated biota in Alfred Crosby's terms, and this often gave them great advantages in changing environments."

Conventional wisdom turned on its head: A new study comparing physical activity and energy expenditure in different populations found that hunter-gatherers burn the same number of calories in a day as their western counterparts living in industrialized settings. This is despite the fact that the hunter-gatherers were more physically active. (Photo: Nico Tondini/Getty Images.)

Others, assuming severe food shortages are a recent phenomenon, have questioned whether famines were frequent enough to explain the evolution of a thrifty phenotype. John Speakman from the University of Aberdeen says, "With a famine rate of 1/150 years there have probably been less than 100 selection events. It is simply impossible for the alleles to have spread in this number of selection events unless they have a massive impact on survival or fecundity." Speakman and others, including Prentice *et al*., doubt whether famines confer a significant survival advantage to the overweight/obese, citing data from famines in recent human history, such as in China resulting from Mao Tse Tung's Great Leap Forward campaign. Data from this famine show that starvation was a rare cause of death in reproductive-age adults, and that mortality mostly falls on the old, who are past reproductive age, and the young.

So, if increased survival can be ruled out as a potential advantage of the thrifty genotype, this leaves the other component of fitness: fecundity. Prentice *et al*., for example, argue that the thrifty genotype may help preserve fertility during famines, conditions where one normally sees a drop in reproduction. Indeed, if one looks at the Great Leap Forward famine, there was a dramatic drop in birth rate, and this is consistent with data from other famines. However, Speakman has argued that there is a dramatic rebound in birth rate that compensates for the famine period, and thus there is no net effect on reproduction. In sum then, assuming that the human populations exposed to such famines exhibited an appreciable rate of obesity — perhaps a tenuous idea to begin with — it's difficult to find strong evidence in favor of the adaptive scenario embodied in the thrifty gene hypothesis.

As an alternative, Speakman has put forward a non-adaptive scenario — the drifty gene hypothesis. According to this idea, genetic drift — the change of gene frequencies due to random, non-selective processes— could explain the current incidence of obesity seen in modern, industrialized populations. Speakman has hypothesized that the threat of predation on early humans may have provided a strong selective pressure to keep maximum body weight in check. A human fleeing from a saber-tooth cat, for example, would be at a clear disadvantage if they carried extra weight. The introduction of fire and cooperative social groups may have reduced the threat of predation, allowing upper body weight to wander through genetic drift. The effects of genetic drift are most profound in small populations, but Speakman argues that just such a process could explain the accumulation of mutations in the human population that affect body weight.

Future outlook

Testing ideas such as the thrifty and drifty gene hypotheses will depend greatly on a better understanding of the genetic basis of obesity. There is no doubt that genetics factors heavily, as it is has been estimated that 40–70% of the variability in body-mass index can be explained by genetic differences. As in other polygenic traits studied, however, the contribution of the few genes identified appear to be rather small. Such genes, satisfyingly, appear to be involved in the signaling pathways that control feeding and energy storage. As more genes are identified, it will be interesting to see if there is any evidence that natural selection has operated on obesity genes or whether, if Speakman is correct, neutral evolutionary processes were at work. However, given that most genes have many different functions, the existence of such genes in the population may after all also reflect selection on a completely different trait than body mass.

Whatever progress is made on the genetics of obesity, it is clear that environmental factors are equally crucial. That obesity was rare in the US and elsewhere nearly a century ago makes this obvious. Something in our environment has conspired with our genes to produce the current situation. As noted, the animal work suggests that the influx of energy-dense food, characterized by high fat and refined sugars, is likely to induce obesity. But what about the claim that our couch-potato lifestyle is a contributing factor? Surprisingly, recent research calls this idea into doubt. In June, a paper from Pontzer and colleagues (PLoS ONE (2012) *7*, e40503) reported that the average daily energy expenditure of a hunter-gather group, the Hadza people living in East Africa, is not significantly different from that of numerous industrialized populations, including Americans. This is despite the fact that the Hadza, as expected, are much more physically active than their western counterparts.

Why this should be is uncertain, but if the results hold up, it suggests that diet rather than physical activity may be a more important component of obesity. Sadly, this is consistent with the demographics of obesity, as the poor, for whom a high-fat diet is the cheapest option, exhibit the highest rates of obesity. In some ways it seems we are a victim of our own success. Advances in agriculture and food processing has brought an abundance of cheap food to the table. Thus, while many in the world are malnourished, industrialized nations have swung to the other extreme, but in the process we have forgotten that the quality of the food is just as important as the quantity.

Turning back to the question of the link between our evolutionary history and obesity, there are no clear answers as yet. We do know that humans have evolved in response to the food in their environment. What's less clear is whether obesity is best seen as a discordance between previous adaptations and our modern environment, as in sickle cell anemia. There is certainly scope for such disharmony. In particular, our modern culture is changing so quickly, it's difficult to imagine how evolution could keep up, especially given that modern medicine undoubtedly reduces the main agent of evolution — natural selection. While frightening for most people, perhaps this scenario is comforting for those that have always wished for a simpler life, free of Big Macs, escalators, and work cubicles.

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Rapid population rise bad for our health?

Research suggests that the rapid population growth of our species in the last 10,000 years has produced a kind of genetic variability for which traditional models of population genetics are inadequate. But do the new findings solve the missing heritability problem emerging from genome-wide association studies? And does the phenomenon put our species at risk? **Michael Gross** investigates.

The ongoing 'genome revolution' has had no shortage of discoveries. New methods like genome-wide association studies (GWAS) have raked in hundreds and thousands of associations between genetic traits and medically relevant phenotypes in the last five years. From the headlines reporting new discoveries, one would think that we are living in a golden age of medical research and all our ills will become curable very soon.

However, a much more sober view prevails as soon as one looks at a specific disorder and sums up which fraction of the case number is accounted for by the genetic discoveries. In autism, for instance, the genes linked to the condition so far only explain a single figure percentage of the cases, even though twin studies suggest that the heritability is much higher (Curr. Biol. (2011) *21*, R571–R573). A similar situation is observed for all other complex diseases that have genetic contributory factors, including cancers, diabetes, and heart disease.

Epigenetics may explain part of the heredity that does not show up in linkage studies, and combinations of frequent mutations that individually only have very weak effects may also play a role. However, recent discoveries have pointed a spotlight on a possible explanation that has so far been underappreciated: mutations that are so rare that they fell through the grid in the first systematic searches for medically relevant polymorphisms.

Abundance of rare variants

Several studies published this year have pointed to a surprisingly high